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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,823	08/28/2002	Michel Revel	REVEL=16	1533

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BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,823	REVEL ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12, 14-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicants' after final amendment and arguments filed on 22 February 2005 is acknowledged.

Status of Claims:

1b. Claims 1-8 and 13 have been canceled. Claims 9-12 and 14-15 are pending and under consideration.

2a. Upon further consideration and search, the examiner has decided to withdraw the finality of the previous office action (mailed on 10 October 2004). PROSECUTION IS HEREBY REOPENED.

Claim rejections-35 USC § 112:

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3b. Claims 9-12, 14-15 are rejected under 35 U.S.C. 112, first paragraph, while being enabling for a method of inducing myelination and remylination of Schwann neurons, a method of reducing NMDA-induced Schwann and oligodendrocyte cell death and a method of reducing Schwann cell death caused by deprivation of nerve growth factor (NGF), by providing a chimera of interleukin-6 receptor-interlukin-6 (IL6RIL6), is not enabling for a method of inducing myelination and remylination or reducing NMDA-induced cell death of unknown populations of neurons, or a method of reducing "all possible" neuron cell death caused by deprivation of nerve growth factor (NGF), or

generically treating any neurodegenerative disease state, with structurally uncharacterized IL-6RIL6 chimera. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification discloses *in-vitro* experiments, using Schwann cell line derived form rat sciatic nerve, demonstrating that the IL6RIL6 chimera causes the induction of the transcriptional-activity from MBP promoter by seven fold, (see page 14, lines 1-17). The specification also discloses that the IL6R/IL6 chimera inhibits oligodendrocyte proliferation *in-vitro*, (Example 2 on page 14, lines 20-29 and figure 2). The effect of IL-6R/IL-6 chimera on remyelination of peripheral nerves following axotomy was examined in example 6, which demonstrates that in the presence of the IL-6R/IL6 chimera 2.5 fold increase in the number of myelinated fibers was found at a 2.5-mm distance below axotomy compared to PBS treated controls. Thus, while the instant specification discloses these *in-vitro* experiments pertaining to the effect of the IL6R/IL6 chimera, there is no disclosure of a method of treating a patient suffering from any of the recited diseases.

The instant specification also discloses *in-vitro* experiments demonstrating that the addition of IL6R/IL6 chimera reduces basal forebrain cholinergic cell death induced by NGF deprivation, (see example 10). In contrast, the specification proposes treating patients suffering from traumatic nerve degeneration or suffering from a dymylinating disease of the central nervous system (CNS) or peripheral nervous system (PNS), Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), multiple

sclerosis (MS), (see page 6, lines 1-12). However, no disclosure is provided in the specification of a single subject that is "treated" by administering IL6R/IL6 chimera, nor does it teach how to assess *in-vivo* administration of IL6R/IL6 chimera. The specification also fails to teach how the administration of IL6R/IL6 chimera would effectively treat such diverse disorders. Furthermore, the full scope of the claimed invention encompasses that IL6R/IL6 chimera protects all neurons from NMDA induced cell death or from toxicity caused by the withdrawal of NGF. However, not all neurons express NMDA receptors, nor do all neurons require NGF for survival. Therefore, it cannot be extrapolated from these limited in-vitro experiments for the skilled artisan to practice Applicants' invention of treating these disparate neurological disorders by administering IL6R/IL6 chimera; or a method of inducing myelination and remylination or reducing NMDA-induced cell death of unknown populations of neurons, or a method of reducing "all possible" neuron cell death caused by deprivation of nerve growth factor (NGF). Additionally, the specification does not disclose any disease or disorder caused by lack of NGF.

The instant specification discloses only one *in-vivo* murine model of chronic relapsing multiple sclerosis, (Example 8). However, in example 8, the specification describes dosage and timetable for administering ILR-IL-6 chimera to mice of the SJL/J strain which were immunized with 0.4 mg bovine MBP in incomplete Freund's adjuvant. The specification fails to disclose the result of this regimen. Accordingly, one cannot ascertain whether the IL6R/IL6 chimera resulted in reduction of clinical grade of the affected mice or reduced demyelination of white brain matter.

Furthermore, the instant claims recite numerous neurodegenerative diseases, however, the recited diseases do not have common cause, nor possess common receptors. For Example, in Alzheimer's disease cholinergic neurons in and projecting to the cortex and hippocampus die, while in Parkinson's disease dopamine producing cells in the substantia nigra die off, which are not dependent on NGF for survival. Also ALS patients have impaired motor neurons which are not dependent on NGF for survival. The art acknowledges that although NGF ensures survival of certain peripheral neurons, but many types of nerve cells do not respond to NGF, (see Barinaga, Science Vol. 264, pages 772-773, middle column of page 772). Therefore, it is not predictable from the instant disclosure that IL6RIL6 chimera would have beneficial effect on all the neurodegenerative diseases recited.

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant case, due to the complexity of the neurodegenerative diseases, the fact that the recited diseases do not have a common cause and due to the fact that the instant specification does not disclose any in vivo experiments showing that the IL6R/IL6 chimera is actually used to treat any of the recited diseases, undue experimentation would be required for the

skilled artisan to test whether IL6RIL6 chimera can be used treat "all" or "any"possible neurological diseases or disorders. The instant specification speculates that IL6RIL6 chimera has neuro-protective effect on peripheral neurons, suggesting an activity in neurodegenerative diseases like, e.g. Alzheimer's Disease, Parkinson Disease or ALS (Amyotrophic Lateral Sclerosis), however, beyond these mere speculations, the specification does not demonstrate that IL6RIL6 chimera actually is effective in treating these disease. The specification teaches that IL-6 like CNTF acts through a common receptor system comprising gp130 and that IL6RIL6 chimera has enhanced IL-6 type activity and that it binds to gp130 with much higher efficiency. However, it is unpredictable whether administering IL6RIL6 chimera would have beneficial or detrimental effects. The art teaches that ALS patients receiving CNTF not only had serious side effects, but fared worse on measures of muscle strength than did patients that received placebo, (barinaga, Science Vol. 264, pages 772-773, May 1994, especially page 773, column 1). Moreover, there is no guidance as to how much is an effective dose of IL6RIL6 chimera to treat any of the recited disorders. Also "protecting" encompasses determining in advance if a patient is susceptible to NMDA-induced cell death, however Applicants are not enabled for such.

Finally, the instant claims are drawn to methods of using an IL-6R/IL-6 chimera, however, the instant specification does not disclose which IL-6R/IL-6 chimera is used. The specification states that the IL-6R/IL-6 chimera is a recombinant glycoprotein obtained by fusing the entire coding sequence of the naturally occurring human soluble interleukin-6 receptor δ-val to the entire coding sequence of mature naturally occurring

IL-6, (page 7, lines 19-28). However, it is unclear which valine of the IL-6R is being referred to, or what is the structure of the human soluble interleukin-6 receptor δ-val. A search for human soluble interleukin-6 receptor δ-val did not turn up any results.

The instant specification states that the chimera L6RIL6 used in the claimed method is preferably produced in mammalian cells as described in WO 99/02552, world patent. However, WO 99/02552 patent discloses several IL6RIL6 chimeras, (see pages 7-8). One of the chimeras disclosed in WO 99/02552, is obtained by linking the entire IL-6 molecule (which comprises 212 amino acid residues) to Val112 -Val356 of the IL-6 receptor through a linker peptide, (see figure 11 of the WO 99/02552). WO 99/02552 also discloses the structure of another IL-6R IL-6 chimera that comprises different domains, such as signal peptide, Ig-like domain, cytokine receptor N-domain and cytokine receptor C-domain (see figure 3). Therefore, it is unclear which one of the chimeras disclosed in WO 99/02552 is used in the claimed method. Accordingly, one of ordinary skill in the art would not know from the instant disclosure, whether the claimed chimera is obtained by fusing the entire human IL-6R to the entire human IL-6, and if so whether a linker peptide is used.

Conclusion:

4. No claim is allowed.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
07 February 2006

Eileen B. O'Hara

EILEEN B. O'HARA
PATENT EXAMINER